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Insulinoma – Diagnosis and Treatment

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1. Introduction

1.1 Epidemiology and basic characteristics

Endogenous hyperinsulinism is characterized by repeated hypoglycemic episodes caused by autonomous hypersecretion of insulin produced by adenoma or multiple microadenomatosis originating in the beta-cells of the pancreas. The process is either localized into one or less frequently few solid tumors or is more diffuse within the islets of Langerhans. Endogenous hyperinsulinism is not regulated by plasma glucose and therefore clinical signs of hypoglycemia manifest whenever during the day. The term „organic hyperinsulinism" is sometimes used showing that real endocrine pancreatic disease may be present in comparison with „functional hyperinsulinism" characterized by reactive changes in a consequence of eating habits.

Insulinoma (ICD-08151/1, ICD-08151/3) together with gastrinoma, VIPoma, somatostatinoma, glucagonoma and PPoma are members of nesidioma family which are recognized as neuroendocrine tumors of the pancreas. Some of them produce one hormone only and may therefore cause typical clinical symptoms. However, combined production of hormones may be also found and clinical diagnosis could be difficult when different symptoms would be combined. Positive but weak staining for gastrin or other hormones besides insulin may be sometimes present without any symptoms. On the other hand, neuroendocrine tumor in the pancreas can be described by histological examination in patients without typical clinical symptoms and malignant tumors are then confirmed.

Insulinoma has incidence of 0.05-0.1 cases per 100 000 inhabitants in the Czech Republic (Škrha, 2001) but slightly more (0.4 per 100 000) has been described at the Mayo clinic register (Service et al., 1991). Data may depend on the database availability in different countries. It is predominantly present in women as compared to men. The proportion of insulinoma was around 60 % in women at Mayo clinic whereas our register involves 75 % of women (Service et al., 1991, Škrha et al., 2009). Insulin-producing tumors occur in more than 50 % of neuroendocrine tumors of the pancreas followed by gastrinomas in 30 %, VIPomas in 10-15 % and by others in less than 10 % (Perry & Vinik, 1995).

Solitary adenoma usually occurs in more than 80 % of patients but few adenomas may be sometimes found in different size and stage of development and thus they have not been removed during the first operation (Service et al., 1991). Repeated surgical treatment is then necessary. Multiple adenoma is more frequently present in patients with multiple endocrine neoplasia (MEN I) (Demeure et al., 1991, Fabbri et al., 2010). However, in only few percents of adults the hypoglycemic syndrome has been associated with hyperplasia of the beta-cells (Harrison et al., 1984, Service et al., 1999, Stefanini et al., 1974). It may be caused by neodifferentiation of islet cells from ductal epithelium in the exocrine pancreas. Previously, nesidioblastosis was described in histological finding, more frequently found in newborns or children than in adults (Stefanini et al., 1974). It was suggested to use the term „**hyperplasia of islet cells**" instead of nesidioblastosis because heterogenous descriptions exist (Weinstock et al., 1986). It is supposed that insulinoma and diffuse hyperplasia are two edge variants of hyperfunctional syndrome and some forms exist in between. The genetic background contributing to different histological findings has not been elucidated yet. The above heterogeneity confirms that histological finding need not always correspond with hormonal activity and clinical symptoms. In addition, beta cell hyperplasia contributes to persistent hyperinsulinemic hypoglycemia of infancy, caused by mutations in the islet ATP-sensitive potassium channel, and to non-insulinoma pancreatogenous hypoglycemia in adults (Ouyang et al., 2011).

Insulinoma is usually localized within the pancreas, extrapancreatic tumors (e.g. in duodenum or small intestine) are extremly rare (Service et al., 1991, Škrha, 2001). One case report describes the insulin producing carcinoid of ovary (Morgello et al., 1988). The most of insulinoma cases are benign whereas malignant forms have been described in 5 to 10 % of patients (Perry & Vinik, 1995, Service et al. 1991). However, various forms have been found by histological examination when different stages of angioinvasion were combined with the presence or absence of micrometastases in lymphnodes. It may strongly influence further decision on chemotherapy and follow-up treatment.

2. Diagnosis of insulinoma

The patients with unregulated insulin overproduction develop clinical symptoms associated with hypoglycemia. Two main tasks may be arised to establish proper diagnosis of insulinoma. Firstly, to evaluate correctly clinical picture suspicious from hypoglycemia and, secondly, to prove the association of typical symptoms with low blood glucose concentration. The diagnosis is therefore based on clinical and biochemical finding still before imaging of the process.

2.1 Clinical symptoms

Hypoglycemia may be associated with either neurogenic (adrenergic) or neuroglycopenic symptoms (Dizon et al., 1999) (Table 1). Symptoms are dependent on depth and duration of hypoglycemia. Slightly decreased plasma glucose to 3.0-3.6 mmol/l stimulates catecholamine secretion explaining neurogenic symptoms. They are rare in patients with insulinoma although they may be solely present in up to 10-15 % of patients (Fajans & Vinik, 1989). On contrary, neuroglycopenic symptoms develop when glucose supply to central nervous system is significantly reduced. Manifested symptoms may frequently induce a suspicion of neurologic or psychiatric disorders and the patient admitted to the appropriate department may be treated not seldom like primary neurological or psychiatric disease.

Unsuccessful treatment with psychiatric or neurologic drugs with persisting symptoms needs to be reevaluated and when fasting hypoglycemia is confirmed a suspicion on endogenous hyperinsulinism may be arised.

Symptoms
Neurogenic (autonomous) sweatting, tremor, palpitation, tachycardia, anxiety **Neuroglycopenic** confusion, dizziness, weakness, unconsciousness, blurred vision, amnesia, dysartria, somnolence, cramps, headache, diplopy, parestesia, coma

Table 1. Hypoglycemic symptoms

Hypoglycemic symptoms develop in the fasting state, several hours after the last meal. This is typically in the morning after the overnight fast when neuroglycopenic symptoms may be present. Their manifestation with proven hypoglycemia and improvement after a sweet meal, formerly described as Whipple trias, are great support for clinical diagnosis of autonomous (endogenous) insulin oversecretion. It does not exclude symptoms developing just after the meal ingestion when overstimulation of insulin secretion especially by sugars exists (Del Sindaco et al., 1997, Service et al., 1999). In such cases functional hyperinsulinism may be falsely diagnosed and proper differentiation between functional and endogenous hyperinsulinism needs to be decided (see 3. Differential diagnosis).
Certain neuroglycopenic symptoms are repeated by the single patient during hypoglycemic episodes although they offer very different picture. It has not been explained yet why the same symptoms are always present in the same patient. They may differentiate one patient from the other. On the other hand, the patient can describe if the frequency of episodes would be increased or if their expression would be strenghten. Such information may help to clinician in decision of further examination and treatment. The severity of symptoms correspond to sensitivity of the central nervous system to hypoglycemia but not exactly to hyperinsulinemia which was significantly different in the patients.
Neuroglycopenic symptoms are the crucial point in diagnosis of insulinoma and their careful analysis is considered as the basis for following steps. Their evaluation cannot be substituted by other examination including imagining of the pancreas.

2.2 Laboratory examinations

The estimation of biochemical variables involving plasma glucose and insulin concentrations during development of clinical symptoms may support not only diagnosis, but it may further characterize the severity of the process and therefore the importance of surgical treatment. Severe hypoglycemia and high serum insulin levels should indicate operation without any delay because profound hypoglycemia is dangerous to the patient. In addition, randomly confirmed hypoglycemia during development of clinical symptoms in patient examined by neurologist or psychiatrist may be the only one impuls to send the patient to endocrinologist. When blood glucose is not determined, the patient can be treated on epilepsy or psychiatric disorders several months or even years without significant success and the proper diagnosis of insulinoma is delayed.
Blood glucose concentration associated with neuroglycopenic symptoms can be often found below 2.5 mmol/l in insulinoma patients whereas neurogenic symptoms associated with blood glucose around 3.5 mmol/l frequently exist by functional (reactive) hyperinsulinemia.

However, hypoglycemia was rarely reported without any clinical symptoms when insulinoma was later confirmed (Service, 1995).
Suspicion on insulinoma suggested from clinical symptoms of neuroglycopenia and hypoglycemia needs to be further confirmed. This first step in diagnosis of endogenous hyperinsulinism may be done by GPs as well as by specialists in neurology, psychiatry, internal medicine or endocrinology/diabetology. Diagnostic process is then simplified if the patient would be sent immediately to appropriate center specialised in endocrine disorders.

2.2.1 Fasting test

Patient with a suspicion on insulinoma is admitted to hospital to confirm the autonomous hypersecretion of insulin as a typical feature of insulinoma. The best option for this purpose is to use the test inhibiting insulin secretion because the absence of insulin inhibition confirmes dysregulation of the hormone secretion by autonomous process. This may be proved by prolonged fasting when the patient drinks only water and blood samples for glucose, insulin and C-peptide determinations are drawn in regular interval (every 4-6 hours). Plasma glucose drops down during the test and when clinical symptoms develop, the last blood sample is drawn and the fasting is stopped. Some delay of clinical symptoms following the lowest plasma glucose concentration may be sometimes present. It is elucidated by later decline of intracellular glucose in the brain in comparison with the changes in plasma glucose concentration. Due to activated contrainsulary hormones by hypoglycemia blood glucose concentration goes already up when symptoms develop in a consequence of the lowest intracellular glucose concentration.
The fasting test may be performed up to 72 hours but in the most of patients it is stopped within 24 hours. At our department we could stop the test within 24 hrs in more than 80 % of patients with insulinoma (Škrha et al., 2009). In some very rare insulinoma cases no neuroglycopenic symptoms have been observed still after 72 hrs (Jordan & Kammel, 1976). The patients with insulinoma are adapted on low glucose concentration and symptoms are therefore weak. Typical picture of hypoglycemia unawereness develops (Mitrakou et al., 1993). Plasma glucose and insulin concentrations are always used in clinical practice in diagnosis of insulinoma but sometimes the ratio of serum insulin/glucose concentration may further support diagnosis of endogenous hyperinsulinism. The results may be more expressive when the patient would add the physical training during the fasting. In subjects with insulinoma plasma glucose concentration drops whereas in those with functional hypoglycemia the glucose concentration may arise (Fajans & Vinik, 1989). Our results obtained in 114 patients with endogenous hyperinsulinism are shown in Table 2.

Laboratory variable	Before fasting	End of fasting
Duration of fasting (h)	-	18 (2-60)
Plasma glucose (mmol/l)	3.4±1.4	1.7±0.4
Seum insulin (mU/l)	54±37	56±47
Insulin/glucose ratio (mU/mmol)	18.5±15.3	34.0±30.3
C-peptide (nmol/l)	1.13±0.61	1.16±0.73

Table 2. Biochemical variables in insulinoma patients before and at the end of fasting test. The results are expressed as the means ± SD.

Glucose and insulin in the fasting test

The patients with endogenous hyperinsulinism have plasma glucose concentration at the end of the fasting test below 2.5 mmol/l but in some cases slightly higher levels may be seen, especially when the lowest level was reached still before developed neuroglycopenic symptoms. In about 7 % of normal population plasma glucose concentration after 72 hrs of fasting may be below 2.7 mmol/l (Service et al., 1999). Evaluation of both glucose concentration and clinical symptoms is therefore recommended.

Majority of patients with insulinoma has increased serum insulin concentration when fasting is stopped. However, in some patients the insulin concentration remains within the normal limits and it brings difficulties to confirm diagnosis of hyperinsulinism (Škrha et al., 2009). Evaluation of all insulin concentrations and their oscillations during the fasting is necessary. In our group of insulinoma patients the insulin concentration below 20 mU/l were found in 12 of 114 patients (10 %) at the end of the test.

The insulin/glucose ratio is also sensitive parameter although it reflects the fluctuations of both biochemical variables. Their dynamic changes causing stepwise increase of this ratio during the fasting test differ from obese patients with hyperinsulinemia who have the ratio increased at the beginning but its decreasing value may be found during the test. Numerical value of the ratio has to be compared with clinical finding during the test. The normal values in our population when glucose is expressed in mmol/l and insulin in mU/l are below 6,0 mU/mmol. We found borderline values of this ratio in 5 of 114 patients with insulinoma.

According to our experience, the most important for the diagnosis of insulinoma is time development of plasma glucose concentrations associated with neuroglycopenic symptoms manifesting during the fasting test.

C-peptide and proinsulin

Serum C-peptide concentration is increased in insulinoma but the basal values cannot be distinguished from those found in obese persons. Its concentration decreases with fasting in healthy persons but it remains high in patient with insulinoma. C-peptide values may provide better information at the end of fasting than at basal state. In addition, C-peptide has to be used when suspicion on hypoglycemia factitia has been arised (see 3. Differential diagnosis).

Higher plasma proinsulin concentration depending on the greater proinsulin release from the beta cells is sometimes determined in insulinoma patients. It may be usefull especially in cases with normal insulin concentration. Proinsulin is not routinelly used for diagnosis of insulinoma and it cannot distinguish benign and malign forms of insulinoma (Fajans & Vinik, 1989).

2.2.2 Suppressive and stimulating tests

Different tests either suppressing insulin secretion or stimulating insulin release and consequently changing plasma glucose concentrations have been used (C-peptide suppressive test, tolbutamide test, calcium test etc.) previously mainly for the research purposes (Fajans & Vinik, 1989, Service et al., 1992). However, they do not significantly improve the diagnosis in routine clinical practice.

In conclusion, diagnosis of endogenous (autonomous) hyperinsulinism has to be done from clinical symptoms and biochemical results. If any doubts would exist, repeated fasting test may bring better data for proper diagnosis than the other tests. The evaluation should also respond key question concerning the treatment. Insulinoma should be treated by surgical removal of the tumor and this procedure needs to localise the tumor before the surgery.

2.2.3 Insulin sensitivity

Repeated attempts have been made to elucidate the estimation of insulin sensitivity in diagnosis of insulinoma (Gin et al., 1987, Nauck et al., 1990, Škrha et al., 1996). Hyperinsulinemic clamp technique enabled to study insulin action both in the hormonal hyperactivity and following the removal of the tumor (Škrha et al., 1993). The amount of glucose infused during the clamp and maintaining the plasma glucose at constant level by exogenous insulin infusion was found increased in insulinoma patients as compared to healthy persons (Gin et al., 1998). The amount of glucose infused dropped down after removal of the tumor. Constant infusion of insulin during the clamp resembles C-peptide suppressive test causing a decrease of endogenous insulin and C-peptide secretion. Impaired suppressibility of C-peptide was found in insulinoma patients compared to healthy controls (Yki-Järvinen et al., 1984).

However, similar non-suppressibility of C-peptide was found in obese Type 2 diabetic patients (Škrha et al., 1996). Insulin resistance was found in insulinoma patients by clamp technique (Del Prato et al., 1993, Nankervis et al., 1985, Škrha et al., 1989, de Kreutzenberg et al., 1995). Decreased insulin clearance and decreased glucose production in the liver contributing to fasting hypoglycemia were observed in insulinoma patients (Škrha et al., 1989, Del Prato et al., 1993). However, we found in some of insulinoma patients nearly normal insulin action and we concluded that this parameter depends on concomitant obesity which may strongly impair the insulin sensitivity (Škrha et al., 1996). Decreased insulin sensitivity cannot be used as reliable sign of insulinoma. Hyperinsulinemic clamp technique can differentiate between patients responding and non-responding to diazoxide treatment (Škrha et al. 1989).

2.3 Localization techniques

Several techniques involving non-invasive and invasive tests may be used to localize the insulinoma with different sensitivity and specificity. They have both advantages and disadvantages. Significant development of imaging technique during the past twenty years has contributed to better localization of insulinoma and thus to preoperative decisions.

Simple **transabdominal ultrasonography** does not bring useful information because of the great number of negative data. Although it is noninvasive and simply performing its low sensitivity, mainly due to minimal discrimination of the small size tumor tissue from the surrounding tissue, it cannot be used for localization of the tumor. Only up to one third of the tumors may be found by this imaging (Bottger et al., 1990).

Computer tomography is very popular but large differences exist between the centers (Pasieka et al., 1992, Vinik et al., 1991). Positive results may be obtained in 25-60 % depending on the experience of radiologists. Similar may be true for **nuclear magnetic resonance** when insulinomas were proved in low or high percentage of the patients (Liessi et al., 1992). In a recent study the sensitivity of preoperative CT and nuclear magnetic resonance was 62 and 82 %, respectively (Varma et al., 2011). **Octreoscan** based on the binding of isotope-labelled somatostatin with its receptors placed on the cell membrane of neuroendocrine tumor was repeatedly used to visualize the localization of insulinoma. However, differences were found between the cells possessing somatostatin receptors. About 50 % or less cases of insulinoma can be proved by octreoscan whereas more than 70 % positive cases with gastrinoma have been found (Krenning et al., 1994, Proye et al., 1998, Zimmer et al., 1996) by using this technique. Octreoscan does not seem to be reliable method detecting localization of insulinoma.

Better results have been obtained with **endoscopic ultrasonography**, sensitivity of which was described in 77 till 94% (Glover et al., 1992, Roesch et al., 1992, Varma et al., 2011). Insulinoma localized in the head and body of the pancreas can be preferably proved by this technique whereas tumors of the tail remain often not discovered. More invasive examination is **arteriography** visualizing vasculature of the pancreas. Finding of pathologic imaging during parenchymal phase may support diagnosis of insulinoma (Fig.1). Positive results have been found in 40 to 60 % in different centres (Pasieka et al., 1992, Vinik et al., 1991). Combining arteriography and CT is superior to single arteriography or CT (Li et al., 2010). In case of successful fine needle aspiration the tumor can be verified with cytopathology examination or by immunocytochemistry (Fig. 2)

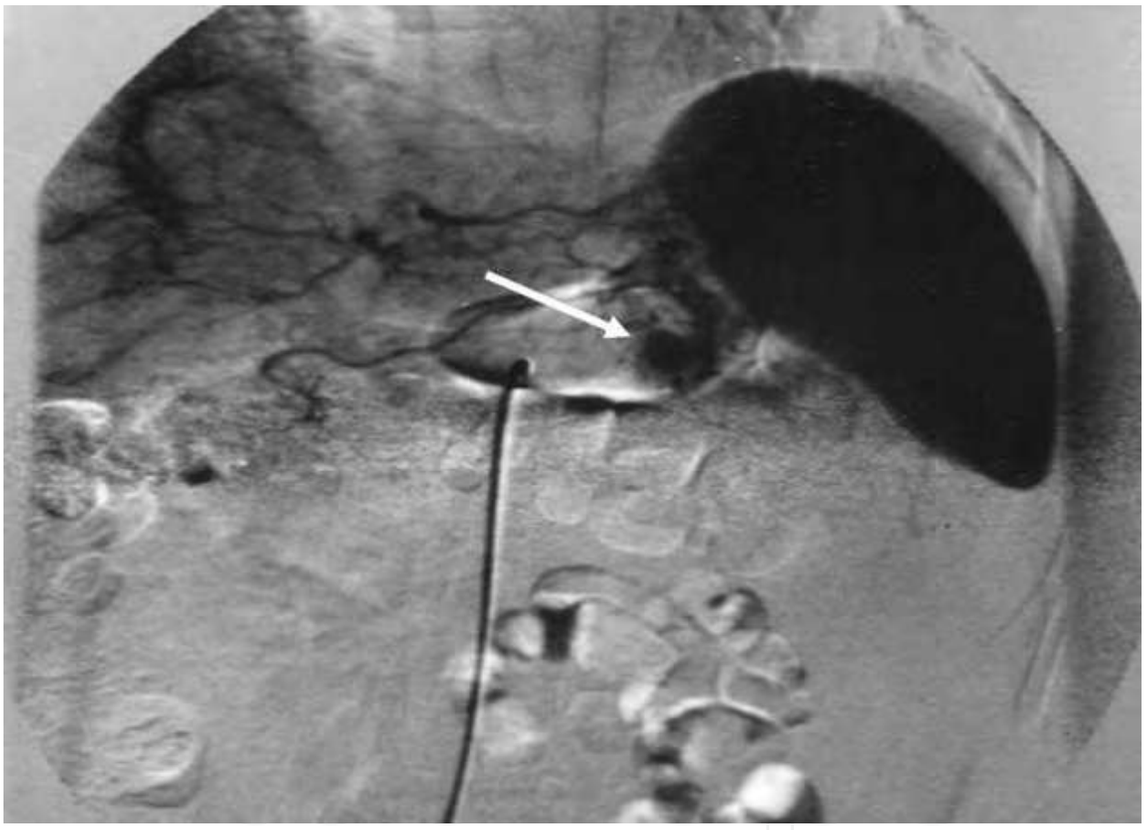

Fig. 1. Digital subtraction angiography of splenic artery with insulinoma localized in the tail of pancreas (arrow)

Some centres use **transhepatic cathetrisation of the portal system** when blood samples drawn by catheter from different parts of portal vein are tested for insulin concentration (Vinik et al., 1991). The main goal of this examination is to differentiate between head, body and tail of the pancreas as a source of measured insulin gradient. The results may be strenghten when calcium is selectively infused into different arteries (superior mesenteric artery, splenic artery or gastroduodenal artery) and blood is taken from the portal system (Doppman et al., 1995). Few centres received very positive results (Vinik et al., 1991).

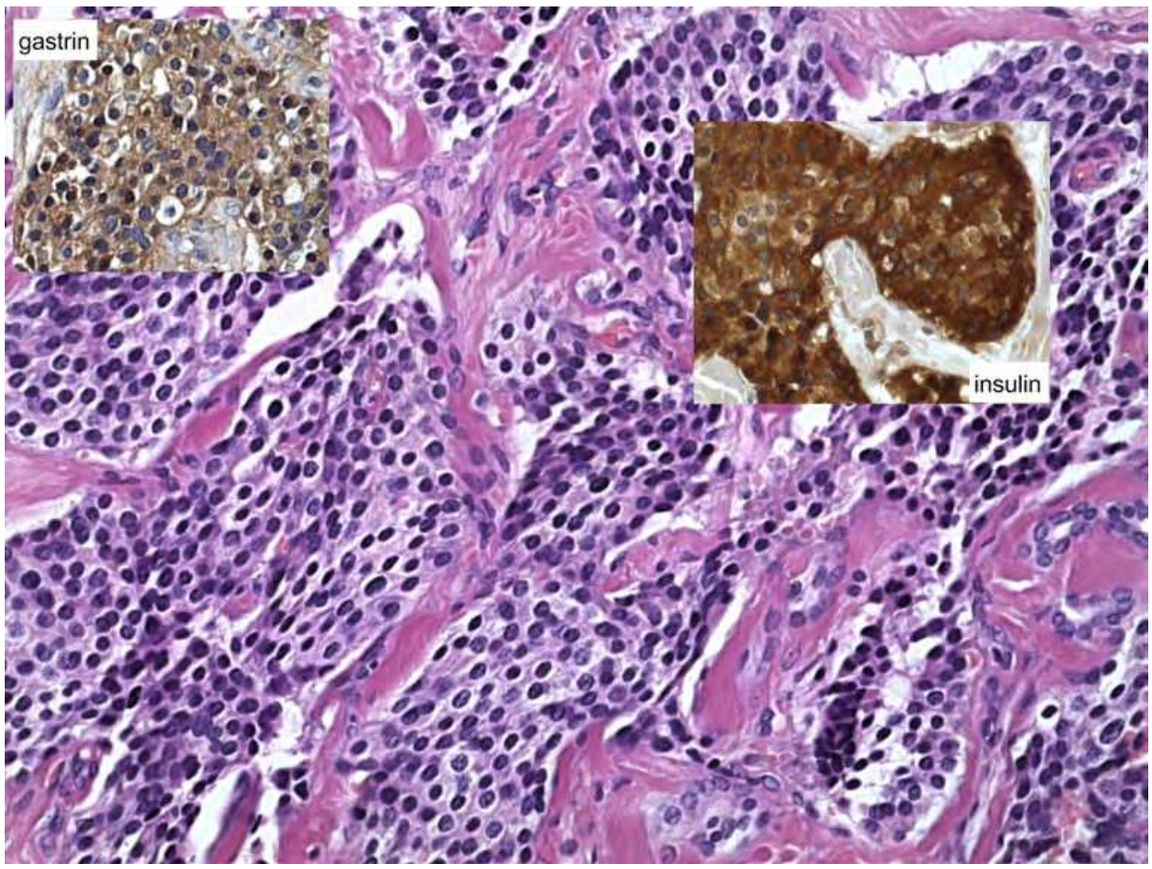

Fig. 2. Histological picture of insulinoma. Immunohistochemical examination found strong positivity of insulin and weak positivity of gastrin.

Our own results of localization of insulinoma are shown in Table 3. In 72 of 103 operated patients (70 %) the topographical localization of the tumor was only done before surgical treatment by combining different techniques when evaluating patients from the whole period of three decades.

Method	Imagine techniques (before surgery)		Surgical finding in preoperatively detected insulinoma		
	Detected	Undetected	Agreement	Other placement	Undiscovered
US	4 (8 %)	47 (92 %)	2	-	2
EU	40 (83%)	8 (17%)	33	5	2
CT	20 (24%)	65 (76%)	15	5	-
AG	39 (43%)	52 (57%)	25	8	6

Table 3. Preoperative localization of insulinoma and surgical finding by preoperatively localized tumors

The transabdominal ultrasonography was tested at our department between 1980-1995 but positive results were extremely rare. This method is not more used in diagnostic algorithm. The quality of CT has been significantly improved during the past twenty years and present

results are better then three decades ago (nearly 50 % positive cases in the last decade). However, when evaluating all patients together, positive results are low (see Table 3). Localization of insulinoma was confirmed in only 75 % of patients with positive CT scan. Angiography brought positive results in more than 40 % but the agreement with localization of the tumor during operation was done in only 64 % of positive findings. Method of choice seems to be endoscopic ultrasonography which detected more than 83 % of tumors and their localization was confirmed in the same proportion (82,5 %).
The results of imaging techniques depend on both size and properties of the insulinoma related to surrounding tissue as well as on the experience of examining staff. Best results have been observed by combining CT with endoscopic ultrasonography. In 2001-2010 we examined 51 patients with insulinoma and positive results of imaging techniques were obtained in 38 of them (75 %).

3. Differential diagnosis

Diagnosis of insulinoma has to be evaluated in consideration of all causes associated with hypoglycemia. Several classifications of hypoglycemic states exist but for clinical purposes combination of two of them is reliable. Firstly, association with ingestion of the meals can differentiate two main groups: a) hypoglycemia developing in the fasting state, typically after an overnight fast, and, b) postprandial hypoglycemia. Secondly, hypoglycemia can be classified according to pathogenesis when balance between glucose influx into blood stream and its removal would be impaired. Both classifications can be combined and diagnosis in the respective patient may be based on detailed analysis of history and symptoms (Table 4).
Evaluation of history of hypoglycemic episodes can disclose when symptoms have developed. It is the basis of clinical classification if hypoglycemia could be found either by healthy person or by ill patient already treated for some disease (Service, 1995). Specific case may be arised when first hypoglycemia episode develops during the stay at hospital.

3.1 Hypoglycemia manifesting predominantly in the fasting state

Hypoglycemia manifesting after an overnight fast needs carefull analysis because it demonstrates that the patient cannot maintain spontaneously plasma glucose concentration within the normal ranges. This condition is frequently caused by certain disease which needs to be elucidated or confirmed. Some clinical diagnoses may be a signal of serious prognosis and their knowledge and intensive treatment is therefore necessary. Both impaired glucose production and accelerated glucose utilization may participate on development of mild or severe hypoglycemic episodes (Table 4).

i. Fasting hypoglycemia
States with diminished glucose production
- lack of contrainsular hormones - enzyme defects - liver disease - renal failure - impaired nutrition - alcohol consumption

ii. Fasting and postprandial hypoglycemia
States with accelerated glucose utilization
Exogenously caused hyperinsulinism
- diabetes treated with insulin - diabetes treated with oral agents - hypoglycemia factitia
Endogenous hyperinsulinism
- insulinoma - hyperinsulinemic hypoglycemia in infants - autoimmune syndromes causing hypoglycemia - extrapancreatic tumors - defects in oxidation of free fatty acids - drugs other then primary oral hypoglycemic agents - other conditions
iii. Reactive (postprandial) hypoglycemia
- alimentary, postoperative - functional - prediabetes - inborn errors of metabolism (enzyme defects) - newborn of diabetic mother

Table 4. Classification of hypoglycemic states according to the relationship with fasting and with underproduction or overutilization of glucose

Hypoglycemia due to diminished glucose production

Plasma glucose concentration depends on permanent glucose supply into the blood stream and removal by the cells using glucose as a simple source of energy. Glucose can be relased from glycogen or it is produced by gluconeogenesis. The glycogen stores cover the needs for few hours only whereas gluconeogenesis provided mainly by the liver and kidney depends both on substrate delivery and on metabolic pathways. Each failure may contribute to impaired glucose metabolism and consequently to lower plasma glucose concentration. Defects in glucose production may be caused either by some chronic diseases (chronic liver and kidney diseases etc.) or by exogenous factors like alcohol or drugs.

Lack of contraregulatory hormones like glucagon, catecholamines, growth hormone and cortisol manifesting by development of insufficiency in the respective organ is associated with mild hypoglycemia in the fasting state. Inborn **hypopituitarism** is characterized by fasting hypoglycemia, low plasma insulin levels, increased insulin sensitivity in the peripheral tissues, diminished responsiveness on hypoglycemia and lowered mobilization of free fatty acids. Similar features have been found in aquired hypopituitarism as well (Samaan, 1989). **Adrenal insufficiency** is associated with impaired mineral metabolism, low blood pressure, weakness and mild hypoglycemia. Untreated **hypothyroidism** develops impaired gluconeogenesis when mild hypoglycemia develops.

Inborn errors of metabolism characterized by enzyme defects are associated with fasting hypoglycemia. This group contains glycogen storing disease, galactosemia and hereditary fructose intolerance (Talente et al., 1994, Tsalikian & Haymond, 1983).

Severe **acute hepatitis** needs intensive treatment with glucose whereas **chronic liver disease** frequently develops mild hypoglycemia. Multiple metastases may be associated with low plasma glucose because both diminished glucose production and accelerated glucose consumption by the tumor may contribute to impaired glucose balance (Eastman et al., 1992). **Renal failure** is associated with mild hypoglycemia and diminished gluconeogenesis in the kidneys was proved (Garber et al., 1974). Severe hypoglycemia may be developed in **malnutrition** by kwashiorkor or anorexia nervosa and hypoglycemic coma may cause death in advanced cases (Ratcliffe & Bevan, 1982).

Special care in differential diagnosis of insulinoma needs to be done to **alcohol induced hypoglycemic episodes**. Alcohol consumption in the evening without substantial meals may be followed by unconsciousness in the morning. Profound hypoglycemia below 2.0 mmol/l may be found in a consequence of diminished glucose production in the liver when glycogen stores were exhausted. Ethanol is oxidized to acetaldehyde which blocks gluconeogenesis. Severe hypoglycemia is then falsely recognized like insulinoma. However, taken history may simply disclose the right cause of this hypoglycemic state. We evaluated several cases of alcohol induced hypoglycemia which was previously diagnosed as suspicion on insulinoma.

Diagnosis of certain disease associated with fasting hypoglycemia needs to be always confirmed because it is of great importance for proper treatment.

3.2 Hypoglycemia manifesting in fasting and postprandial state

The most of hypoglycemic episodes comes both in the fasting and postprandial conditions, typically in diabetic patients. They are caused by overutilization of glucose in the target tissues by increased insulin action.

Hypoglycemia due to accelerated glucose utilization

The most frequent hypoglycemic states are caused by hypoglycemic drugs in diabetic patients. Insulin, sulphonylurea or different combinations of antidiabetic drugs may contribute to hypoglycemia, especially when the patient is intensivelly treated to target values of diabetes control. This issue is specific chapter in diabetes books and it is not analyzed here. Confirmation of drug treatment in diabetic patients may exclude the majority of cases from consideration on insulinoma. However, newly developed repeated hypoglycemic episodes in Type 2 diabetic patient without any evidence on drug involvement have been described and insulinoma was later confirmed (Škrha et al., 1990).

Special attention needs to be done to hypoglycemia in infancy when different types of „persistent hyperinsulinemic hypoglycemia in infancy“ (PHHI) have been described (Stanley, 1997). Congenital hyperinsulinism is a life threatening state in a newborn and sometimes only pancreatectomy may resolve this serious condition (De Lonley-Debeney et al., 1999). In other cases hypoglycemia develops later and more frequently it may be induced by fasting or it occurs between breast feeding (Thornton et al., 1998). Such latent hypoglycemia may be dangerous for development of the central nervous system manifesting by mental retardation. The early diagnosis and effective treatment are therefore absolutely necessary. Diagnosis is supported by hyperinsulinemia and increased plasma C-peptide concentration in hypoglycemic state together with low free fatty acids and beta-hydroxybutyrate (Cresto et al., 1998). In some children hyperammonemia was proven (Kitaura et al., 1999, Stanley et al., 1998). Persistent hyperinsulinemic hypoglycemia in infancy was subdivided into three types (Stanley, 1997).

Rapid development of severe hypoglycemia in a newborn just after delivery is typical by **autosomal recessive form** of congenital hyperinsulinism which is caused by gene mutation for sulphonylurea receptor (SUR1) associated with potassium channel in the beta-cells (Thomas, et al., 1995, Nestorowicz et al., 1996). Persistent insulin hypersecretion is due to closed K_{ATP}- channel and opened calcium channel. Histological picture disclosed two forms – diffuse and focal. Diffuse form called nesidioblastosis has all islets hyperactive whereas the other one is caused by focal hyperplastic adenomatosis (Sempoux et al., 1998). Partial pancreatectomy is sufficient for treatment of focal form but diffuse nesidioblastosis needs to be treated by total pancreatectomy.

Autosomal dominant form is usually manifested later following months or even years and clinical symptoms may be induced by fasting (Thornton et al., 1998). Drug treatment with diazoxide is often effective. Glucokinase gene mutation was found in this form (Glaser et al., 1998) and it is evident that recessive and dominant forms are totally different not only by gene determination but by treatment as well.

Hyperinsulinemic hypoglycemia with hyperammonaemia is the third form characterized by gene mutation of mitochondrial glutamate dehydrogenase. Increased alpha-ketoglutarate production stimulate insulin secretion whereas ammonium detoxification by lowered glutamate supply into liver causes hyperammonaemia (Zammarchi et al., 1996, Stanley et al., 1998, Kitaura et al., 1999).

Modern polypills treatment contributes to drug interactions. It may be therefore important to summarize which drugs accelerate the hypoglycemic effects of sulphonylurea drugs in Type 2 diabetes (Table 5).

a.	Sulphonylurea release from the binding with albumin - salicylic acid, acetylsalicylic acid - nonsteroid antiflogistics - sulphonylamides - trimetoprim - fibrates
b.	Competitive inhibitors of sulphonylurea metabolism - alcohol - H_2 – blockers - sulphonylamides - anticoagulant drugs - pyrazolon derivatives - allopurinol - inhibitors of monoaminooxidase
c.	Inhibitors of sulphonylurea excretion - probenecide - acetylsalicylic acid - nonsteroid antiflogistics - allopurinol - sulphonylamides

Table 5. Drugs accelerating the effects of sulphonylurea derivatives with possible hypoglycemia development

Arteficially induced hypoglycemia by using hypoglycemic agents, especially insulin or sulphonylurea derivatives, are clasified as **hypoglycemia factitia**. Severe hypoglycemia with neuroglycopenic symptoms may develop and clinical picture is fully comparable with insulinoma, mainly when hypoglycemia would be detected in fasting state. Clinical symptoms associated with profound hypoglycemia and hyperinsulinemia may be summarized as insulinoma and because no tumor localization is done, an exploratory laparotomy is indicated. The cause of hypoglycemic drug administration in non-diabetic subjects may be undiscovered but sometimes mental or psychiatric problems are present. Health care personel (nurses, physicians etc.) between this drug abuse has been repeatedly found.
Insulin administration may decrease endogenous secretion of both insulin and C-peptide. Finding of increased serum insulin concentration together with decreased C-peptide levels may support suspicion on hypoglycemia factitia. More difficulties bring sulphonylurea derivatives because no suppresion of C-peptide is present and low drug plasma or urine concentration is often missed. In such cases, proinsulin may be used to exclude diagnosis of hypoglycemia factitia because its plasma concentration in this case is within the normal limits whereas it is increased in insulinoma patients (Table 6).
We examined five patients with hypoglycemia factitia sent to our department as a suspition on insulinoma. One of them was nine times admitted to the hospital and twice indicated for exploratory laparotomy before the Münchhausen syndrome was confirmed.

Laboratory variable	**Insulinoma**	**Hypoglycemia factitia caused by insulin**	**Hypoglycemia factitia caused by sulphonylurea**
Plasma glucose	↓↓↓	↓↓↓	↓↓↓
Plasma insulin	↑ - ↑↑↑	↑↑↑	↑↑↑
Serum C-peptide	↑ - ↑↑	↓ - ↓↓	↑ - ↑↑
Plasma proinsulin	↑ - ↑↑	↔	↔
Sulphonylurea (urine)	negative	Negative	positive

Table 6. Laboratory variables compared in insulinoma patients with hypoglycemia factitia subjects

Other conditions may contribute to increased glucose removal from the blood stream but they are rare and single patients have been reported like case reports. Insulin antibodies or insulin receptor antibodies were rarely associated with hypoglycemia (Redmon et al., 1992, Service 1995, Walters et al., 1987). Extrapancreatic (non-islet cells) tumors like leiomyosarcoma, fibrosarcoma, mezotelioma, hepatoma and different cancers may be associated with hypoglycemia but with normal or low insulin concentration. In some of them increased plasma concentration of IGF-2 or „big-IGF-2" has been observed. High insulin levels were found in fibrosarcoma, bronchial carcinoid, neurofibrosarcoma and small cell cervical carcinoma. In such cases insulinoma is considered until ectopic insulin production would be confirmed. Different clinical picture and progression of malignant disease may differentiate these patients from those with insulinoma.
Rare carnitine deficiency is associated with impaired beta-oxidation of fatty acids. In such situation the organism cannot yield energy from fatty acids and alternative substrate like glucose is then utilized. Substrate deficit caused by blocked beta-oxidation creates consuption of glucose with severe hypoglycemia (McGarry & Foster, 1980).

Hypoglycemia may be caused by other drugs which stimulate insulin secretion (chinin) or decrease glucose production (beta-blockers, salicylates) or induce complex of not fully discovered mechanisms (haloperidol, disopyramide, pentamidine). Glucose consumption by Plasmodium falciparum was observed in malaria.

3.3 Reactive hypoglycemia

Reactive or postprandial hypoglycemia is a common diagnosis associated with weakness and other neurogenic (adrenergic) symptoms. The patient thinks on a serious disease and asks for help. Correct diagnosis and simple recommendation of reliable regimen including dietary councelling may totally remove the symptoms. In patients after gastric surgery when the meals containing saccharides quickly stimulate insulin secretion, glycemia drops down in 30 to 60 min. Sweating, tachycardia a weakness develop and only omitting of sweets may significantly improve the patient´s clinical state. Similar symptoms caused by sweets ingested in the morning develop mainly in some young women who do not eat typical breakfast. No previous operation on gut has been done by them before. They frequently do not take breakfast but after coming to their office they eat sweets like chocolate with coffee or tea. Chocolate without substantial meal induces insulin hypersecretion with small decrease of plasma glucose. Similar pattern may be obtained during oral glucose tolerance test (oGTT) with decreased plasma glucose to 2.9-3.3 mmol/l in 120 or 180 min (Brun et al., 1995). Such condition improves only after dietary recommendation when sweets are omitted. Analysis of symptoms can usually confirm this diagnosis.

Reactive hypoglycemia is frequently considered as insulinoma. In majority of patients neuroglycopenic symptoms are lacking. Hypoglycemia is not confirmed in some patients and the term „pseudohypoglycemia“ is then used. If changes in dietary regimen would not be successful, fasting test is recommended to exclude uncertain cause of the weakness and other adrenergic symptoms. The patient with reactive hypoglycemia has normal glycemia without any significant decrease during the test.

4. Treatment

Recurrent profound hypoglycemia due to insulinoma or autonomous hyperplasia of the beta cells is dangerous to the patients because it may cause acute accidents like stroke or arrythmias, and consequently sudden death, especially with increasing age. They may also initiate chronic deterioration of intelectual function when they are present for a long time. The proper treatment strategy is therefore necessary and individual assessment of the risk has to be evaluated. The causal treatment involves surgical removal of the insulinoma or diffuse hyperplastic beta cell tissue (in case of „microadenomatosis“). When surgery is unsuccessful or the risk of operation is too high in old and polymorbid patient then dietary regimen and drug treatment have to be used (Škrha et al., 2009).

4.1 Surgical treatment

Selective removal of the tumor in case of solitary insulinoma is a method of choice. Enucleation of insulinoma maximally preserving the surrounding pancreatic tissue is now prefered against blind resection (Škrha, 2001) . It needs to have accurate localization of the tumor which enables to decide if laparoscopic technique or classical laparotomy may be introduced. The latter is started by gentle manual palpation of the pancreas, confirming the place with tumor and compares this finding with the results of preoperative imaging.

Perioperative ultrasound may sometimes help in confirming the tumor (Norton et al., 1988). If localization of the tumor would not make possible enucleation due to close proximity of the vessels, resection is decided. Blind resection is no more recommended although in patients with serious hypoglycemias and high hormonal activity it has to be suggested when no localization of the tumor has been done both before or during the operation. Small tumor with diameter below 5 mm may be overlooked and when neither serious symptoms nor high hormonal activity are present it can be better to operate for the second time than to make blind resection. Both types of operations may be subsequently associated with complications. Following resection, subfrenic inflammation causing localized abscess, sepsis or fistulae may be developed (Geoghegan et al., 1994). Fistulae develop sometimes after enucleation as well (Pasieka et al., 1992).

Insulinoma may be localized within the whole pancreatic tissue. However, results from different centres bring various finding (Rothmund et al., 1990). It may be partly influenced by the number of evaluated patients. Some authors describe the predominance of insulinoma within the head of pancreas, the others found regular distribution between all three parts of pancreas. In our group of 103 operated patients we found 93 solitary insulinoma distributed in 30 % in the head, 28 % in the body and 42 % in the tail (Fig. 3). Other two patients had diffuse microadenomatosis, two patients with not proven insulinoma during the first operation were successfully reoperated. Removal of insulinoma is followed by hyperglycemia developing in a consequence of suppressed beta-cell function by insulinoma. Its manifestation in the next day after the operation usually confirms surgical success. In case that hypoglycemia persists postoperatively in spite of removed insulinoma, multiple tumor may be present. In patients with diffuse hyperplasia the total pancreatectomy may sometimes be necessary with subsequent substitution of both exocrine and endocrine functions.

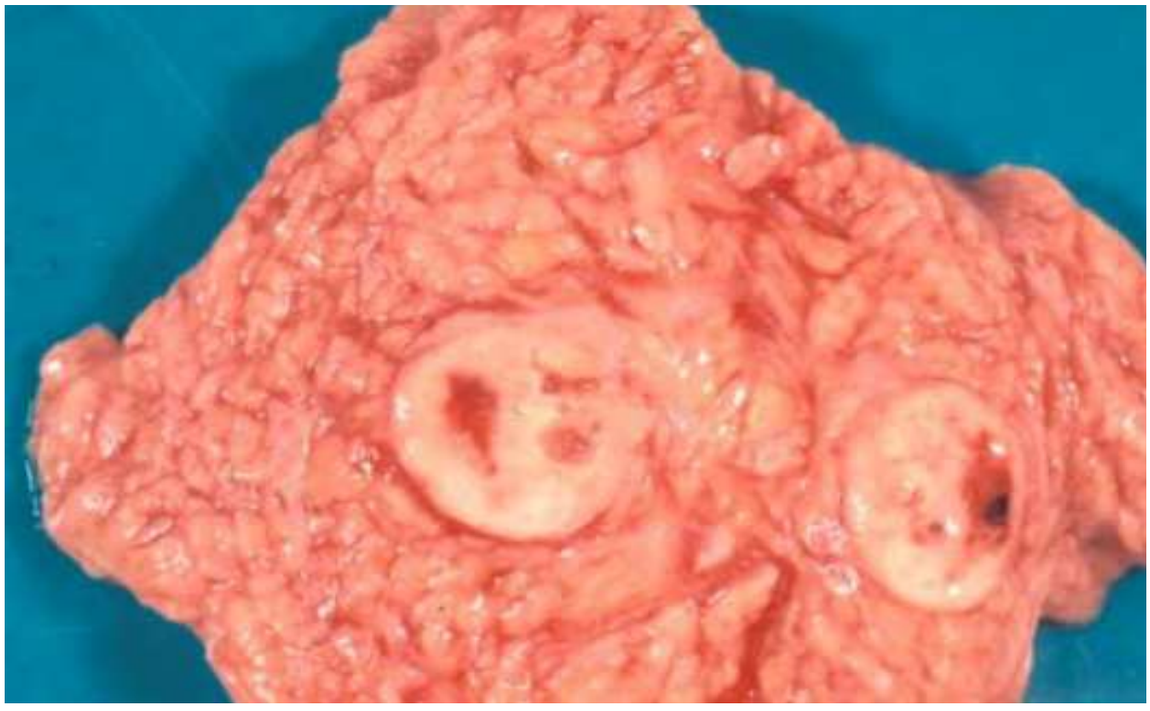

Fig. 3. Insulinoma localized in cut head of the pancreas.

4.2 Conservative treatment

Insulinoma can be operated in every age and therefore high age is not a contraindication. In case of advanced ischemic heart disease with chronic heart failure or clustering with other risks the operation cannot be recommended and the patients are treated conservatively. Diabetic diet excluding free sugars which may induce hypoglycemic attacks is recommended because it does not stimulate insulin secretion like free diet containing sugars. Several doses of meals mainly in the night are sometimes necessary when severe hyperinsulinism has been developed. Free sugars are used during hypoglycemic attack but not in its prevention. Dietary regimen is often combined with the insulin secretion blocking agent (Fajans & Vinik, 1989).

Diazoxide, a thiazide derivative, or somatostatin analogues decrease insulin levels and then hypoglycemic attacks develop less frequently or they are much less severe. Diazoxide acts as potassium channel opener and thus calcium channel is subsequently closed. This blockade of calcium movement in the beta cell lowers insulin secretion. Doses of 3 to 8 mg/kg daily are recommended but in some cases only 100 mg is sufficient to relief the clinical symptoms. Somatostatin treatment uses the presence of its receptors on beta cells which are less frequent than in other neuroendocrine tumors. Such therapy is therefore not so successful as in patients with gastrinoma. Not all patients respond on both drug therapy and then dietary regimen remains as the only one option.

From our group of 113 patients with organic hyperinsulinism total of 103 were operated and remaining 10 were primarily treated conservatively during 10-22 years. Additional 8 patients without removal of insulinoma during the operation have been treated conservatively as well. Interesting information was done when preoperative localization was compared with the finding in surgery. Operation could confirm localization in 80 % (54 of 68) of preoperatively found insulinoma when CT scan, angiography and endoscopic ultrasonography could be combined to visualize the tumors. When analyzing the results of localization of the tumors with surgical finding in 103 operated patients, localization was done in 68 (66 %) preoperatively, in 27 (26 %) cases the tumor was found and removed during the operation and in 8 (8 %) patients no insulinoma was found during the operation. Operation was successful in 92 % of our patients with organic hyperinsulinism.

Malignant insulinoma and its treatment

Malignant insulinoma (ICD-08151/3) occurs in 5-10 % of all insulinoma cases. It grows very slowly and develops typical neuroglycopenic symptoms. When diagnosed and confirmed organic hyperinsulinism it may be found by CT scans like solitary tumor in the pancreas but not seldom with already developed metastases in the lymph nodes or in the liver. Chemotherapy involves combination of streptozotocin with 5-fluorouracil or other cytostatic drugs. It is recommended to combine chemotherapy with surgical treatment with the removal of primary tumor or metastases in the liver. In one of our patient (56 yrs old woman) total pancreatectomy was combined with transplantation of the liver after the liver removal because multiple large metastases have been present. Consequently isolated islets of Langerhans were injected into the portal system using transhepatic cathetrization. One year later the patient does not suffer from any problems. Malignant insulinoma although successfully removed may develop late metastases which are no more hormonaly active.

5. Prognosis

Benign insulinoma are cured by surgical removal and its recurrency is extremely rare. Multiple adenoma in different stage of development may cause repeated hypoglycemia when only one tumor was removed. Conservative treatment with diazoxide may be

successful many years, e.g. in patient with microadenomatosis. The patients after total pancreatectomy have sometimes problems with diabetes and sufficient enzyme substitution has to be added as well. Malignant insulinoma has poor prognosis because of high mortality and the patients die after several years with dissemination of the process.

6. Algorithm of diagnosis and treatment

Our own experience is the background to suggest algorithm of diagnosis and treatment in patients with endogenous hyperinsulinemia (Fig. 4). Analysis of clinical symptoms and biochemical finding of hypoglycemia in the fasting state in patients without any serious disease may serve as the basis for diagnosis of insulinoma. When the diagnosis is confirmed by fasting test the localization of the tumor has to be done. Surgical treatment is a method of choice whereas conservative treatment is followed after unsuccessful operation or in severly polymorbid patients when operation brings high risk.

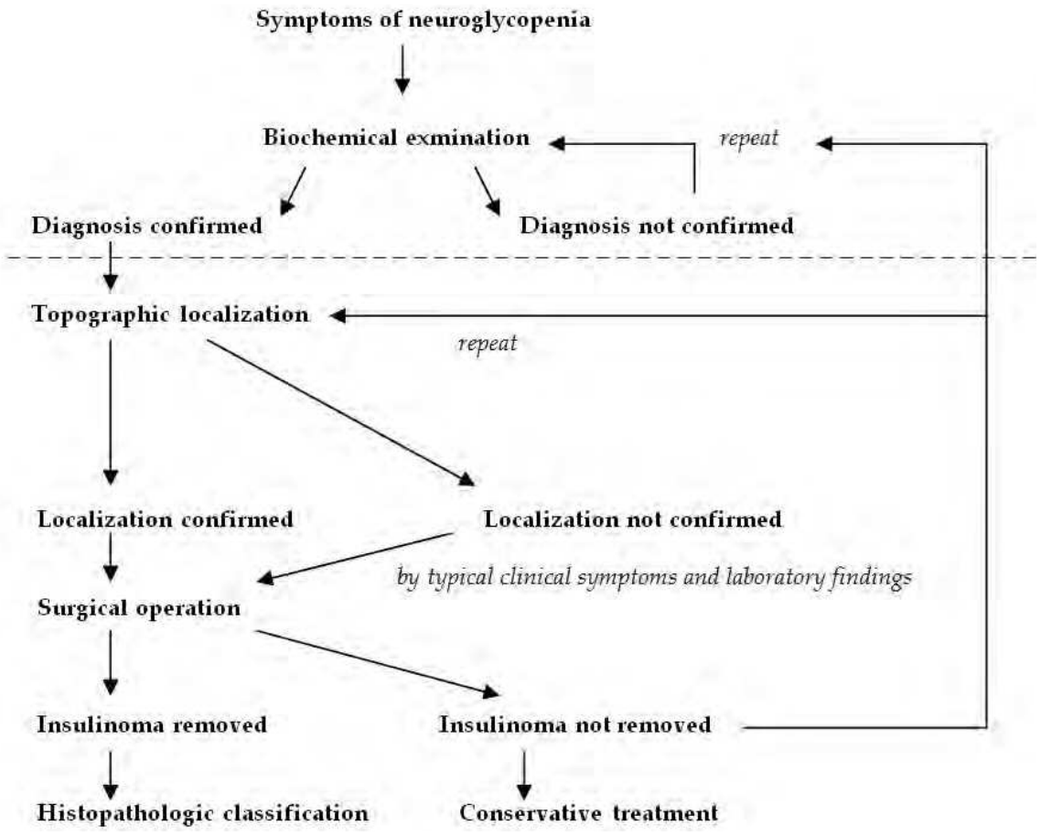

Fig. 4. Algorithm of diagnosis and treatment in patients with suspicion on insulinoma.

The dotted line expresses the level where diagnosis of endogenous hyperinsulinism need to be established and where the operation has to be decided

7. Conclusions

Insulinoma is a rare endocrine disease. Its diagnosis may be sometimes overlooked because clinical symptoms of hypoglycemia may resemble different disease. Better knowledge of

neuroglycopenic symptoms may strongly improve diagnostic process and initiate further examinations. When any doubts on clinical picture exist, detailed differential diagnosis should be performed. Localization of the tumor is recommended just after confirmation that endogenous hyperinsulinism is a source of fasting hypoglycemia. Although the imaging techniques have significantly improved localization of the tumors in the past decade, some tumors have not been localized and exploration by laparotomy has to be done. Primary surgical treatment is a method of choice whereas conservative treatment may be suggested when operation was failed or poor clinical state could bring difficulties to surgical treatment. Follow-up of insulinoma patients is recommended but recurrent tumors are very rare. It may be important especially in cases with signs of perineural invasion or angioinvasion when cytostatic drugs should be decided. Close collaboration with oncological department is then necessary.

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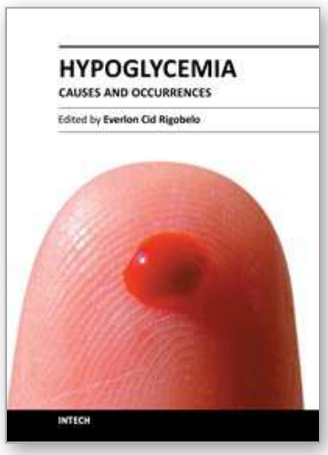

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Glucose is an essential metabolic substrate of all mammalian cells being the major carbohydrate presented to the cell for energy production and also many other anabolic requirements. Hypoglycemia is a disorder where the glucose serum concentration is usually low. The organism usually keeps the glucose serum concentration in a range of 70 to 110 mL/dL of blood. In hypoglycemia the glucose concentration normally remains lower than 50 mL/dL of blood. This book provides an abundance of information for all who need them in order to help many people worldwide.

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